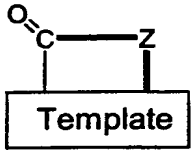
CLAIMS

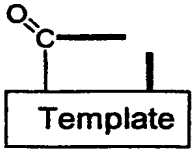
1. A process for the manufacture of compounds of the general formula



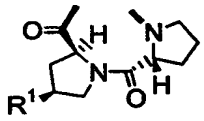
I

wherein

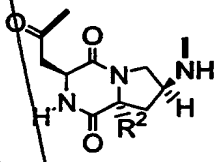
Z is a chain of n α-amino acid residues which, if their α-C atom is asymmetric, have L-configuration, n being an integer from 4 to 20, the positions of said amino acid residues in said chain being counted starting from the N-terminal amino acid;



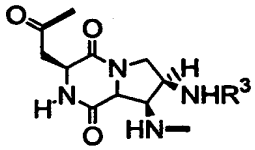
is one of the groups of formulae



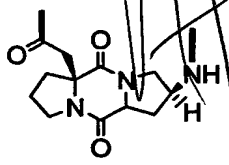
(a)



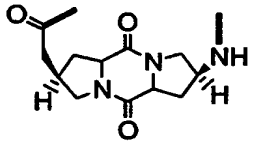
(b)



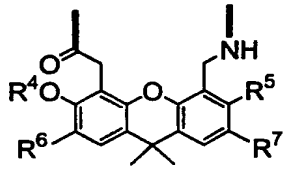
(c)



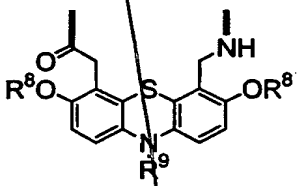
(d)



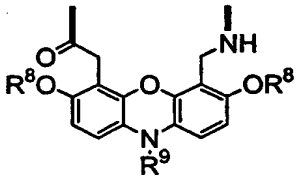
(e)



(f)



(g)



(h)

R^1 is hydrogen or a protected amino group;

R^2 is hydrogen or a group of formula CH_2-$COOR^{10}$;

R^3 is an amino-protecting group;

R^4 is lower alkyl or aryl-lower alkyl;

R^5 is lower alkyl, lower alkoxy or aryl;

R^6 is hydrogen, lower alkyl, substituted lower alkyl, aryl, Br or NO_2;

R^7 is hydrogen, lower alkyl, substituted lower alkyl, aryl, Br or NO_2;

R^8 is lower alkyl, substituted lower alkyl or aryl-lower alkyl;

R^9 is lower alkyl, substituted lower alkyl or aryl-lower alkyl; and

R^{10} is hydrogen, lower alkyl, substituted lower alkyl, aryl, aryl-lower alkyl, aroyl-lower alkyl or allyl;

and of salts thereof, which process comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position $^n/_2$, $^n/_2+1$ or $^n/_2-1$ if n is an even number and, respectively, in position $^n/_2+^1/_2$ or $^n/_2-^1/_2$ if n is an odd number, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

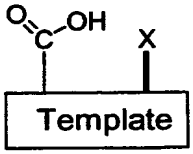
(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position nearer the N-terminal amino acid residue, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product thus obtained;

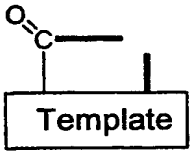
(e) repeating, if necessary, steps (c) and (d) until the N-terminal amino acid residue has been introduced;

(f) coupling the product thus obtained with a compound of the general formula

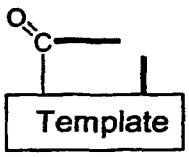


II

wherein

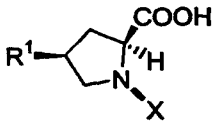


is as defined above and X is an N-protecting group or, if



is to be group (a), above, alternatively

(fa) coupling the product obtained in step (d) or (e) with a compound of the general formula **III**



III

wherein R^1 and X are as defined above;

(fb) removing the N-protecting group from the product thus obtained; and

(fc) coupling the product thus obtained with an appropriately N-protected derivative of D-proline;

(g) removing the N-protecting group from the product obtained in step (f) or (fc);

(h) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is in position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(i) removing the N-protecting group from the product thus obtained;

(j) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product is one position farther away from position n, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(k) removing the N-protecting group from the product thus obtained;

(l) repeating, if necessary, steps (j) and (k) until all amino acid residues have been introduced;

(m) detaching the product thus obtained from the solid support;

(n) cyclising the product cleaved from the solid support;

(o) removing any protecting groups present on functional groups of any members of the chain of amino acid residues and, if desired, any protecting group(s) which may in addition be present in the molecule; and

(p) if desired, converting the product thus obtained into a salt or converting a salt thus obtained into the corresponding free compound of formula I or into a different salt.

2. A process according to claim 1 wherein the functionalized solid support is derived from polystyrene crosslinked with divinylbenzene; from polystyrene coated with polyethyleneglycol spacers; or from a polyacrylamide resin; and is functionalized by means of a linker, i. e. a bifunctional spacer molecule which contains on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformation and cleavage procedures.

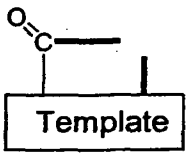
3. A process according to claim 2 wherein the linker forms acid-labile benzyl, benzhydryl or trityl esters with the carboxyl group of the amino acids.

4. A process according to claim 3 wherein a 3-methoxy-4-hydroxyphenylphenoxy (Sasrin), 4-(2,4-dimethoxyphenyl-hydroxymethyl)-phenoxy (Rink), 4-(4-hydroxymethyl-3-methoxy-phenoxy)butyric acid (HMPB), trityl or 2-chlorotrityl linker is used.

5. A process according to any one of claims 1 to 4 wherein X and the N-protecting group of the amino acid derivatives is 9-fluorenylmethoxycarbonyl (Fmoc).

6. A modification of the process according to any one of claims 1 to 5 for the manufacture of enantiomers of the compounds of formula I as defined in claim 1 in which all amino acids which have an asymmetric α-carbon atom are used in their D-Form and the enantiomer of a template corresponding to structure (a), (b), (c), (d) or (e) or a template corresponding to formula (f), (g) or (h) is used in step (f) and, respectively, the enantiomer of a compound of formula III is used in step (fa) and a derivative of L-proline is used in step (fc).

7. Compounds of the general formula I as defined in Claim 1 with the provisos that if



is

(i) group (a) and R^1 is hydrogen, then Z is other than

-Val-Lys-Asn-Tyr-Gly-Val-Lys-Asn-Ser-Glu-Trp-Ile- [SEQ ID NO:9],

-Val-Lys-Asn-Tyr-Gly-Val-Lys-Asn-Ser-Glu-Trp-Thr- [SEQ ID NO:10],

-Gly-Arg-Gly-Asp- [SEQ ID NO:11],

-Arg-Gly-Asp-Gly- [SEQ ID NO:12],

-Phe-Tyr-Thr-Gly-Thr- [SEQ ID NO:13],

-Tyr-Arg-Asp-Ala-Met- [SEQ ID NO:14],

-Asn-Thr-Tyr-Ser-Gly-Val- [SEQ ID NO:15],

-Trp-Asp-Asp-Gly-Ser-Asp- [SEQ ID NO:16] and

-Leu-Trp-Tyr-Ser-Asn-His-Trp-Val- [SEQ ID NO:17];

(ii) group (b) and R^2 is hydrogen or CH_2-COOH, or group (c) and R^3 is benzoyl, or group (d), or group (e), then Z is other than -Ala-Asn-Pro-Asn-Ala-Ala- [SEQ ID NO:18];

(iii) group (b) and R^2 is hydrogen, then Z is other than -Ala-Arg-Gly-Asp- [SEQ ID NO:19];

(iv) group (f), R^4 is methyl, R^5 is methoxy and R^6 and R^7 each are hydrogen, then Z is other than

-Val-Ala-Ala-Phe-Leu-Ala-Leu-Ala- [SEQ ID NO:20],

-Arg-Gly-Asp-Val- [SEQ ID NO:21],

-Ala-Thr-Val-Gly- [SEQ ID NO:22],

-Glu-Arg-Gly-Asp-Val-Tyr- [SEQ ID NO:23],

-Ile-Ala-Arg-Gly-Asp-Phe-Pro-Asp- [SEQ ID NO:24],

-Ala-Arg-Ile-Ala-Arg-Gly-Asp-Phe-Pro-Asp-Asp-Arg- [SEQ ID NO:25],

-Ala-Arg-Gly-Asp-Phe-Pro- [SEQ ID NO:26],

-Arg-Gly-Asp-Phe- [SEQ ID NO:27] and

-Arg-Ile-Ala-Arg-Gly-Asp-Phe-Pro-Asp-Asp- [SEQ ID NO:28];

(v) group (g), R^8 is methyl and R^9 is methyl or n-hexyl, or group (h), R^8 is ethyl and R^9 is ethyl, then Z is other than -Arg-Gly-Asp-Val- [SEQ ID NO:21];

(vi) group (g), R^8 is methyl and R^9 is methyl or benzyl, then Z is other than -Gly-Gly-Ala-Gly- [SEQ ID NO:29];

(vii) group (g), R^8 is methyl and R^9 is methyl, then Z is other than -Gly-Asp-Gly-Gly- [SEQ ID NO:30]; and

(viii) group (g), R^8 is methyl and R^9 is n-hexyl, then Z is other than -Val-Arg-Lys-Lys- [SEQ ID NO:1].

8. The enantiomers of the compounds of the general formula I as defined in claim 1.

Add A2